UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,069	09/24/2004	Anne Simone Josephine Lesage	JANS-0072	3249

45511 7590 05/18/2007

WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	**PAPER NUMBER**
1618	
MAIL DATE	**DELIVERY MODE**
05/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

TH

Office Action Summary	Application No.	Applicant(s)	
	10/509,069	LESAGE ET AL.	
	Examiner	Art Unit	
	Melissa Perreira	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-9,11,13-15 and 17-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-9,11,13-15 and 17-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-4,6-9,11,13-15 and 17-35 are pending in the application. Claims 5,10,12 and 16 have been cancelled and claims 18-35 added in the amendment filed 4/4/07. Any objections and/or rejections from previous office actions that have not been reiterated in this office action are obviated.

Response to Arguments

1. Applicant's arguments filed 4/4/07 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention as stated in the office action mailed 1/8/07. It is unclear as to how much constitutes a therapeutically effective amount or how much is necessary to provide an effective radioactive composition.

4. Applicant asserts that it is clear from the information in the art in combination with applicant's disclosure what a "therapeutically effective amount" would be. Also applicant asserts that examiner Hartley, who is also associated with the examination of the instant application, has allowed claims reciting, "therapeutically effective amount" in several patents.

5. Each application is examined individually and a clear and definite definition of the recitation of "therapeutically effective amount" is inspected for in each disclosure. The disclosure of the applicant does not provide for a clear and definite definition or explicitly point out the description of the recitation of "therapeutically effective amount" in the disclosure.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-4,6-9,15 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cai et al. (US 5,597,922) in view of Freyne et al. (US 5,541,325) as stated in the office action mailed 1/8/07. The modified rejection is necessitated by the amendment to the claims.

8. Applicant asserts that Cai et al. describes compounds that exhibit glycine receptor antagonist activity.

9. Cai et al. teaches of the glutamate/NMDA receptors which bind both glycine and glutamate as well as their antagonists (column 1, lines 41-43). The binding of the glycine receptor antagonists of the disclosure is a diagnostic method for detecting the presence of NMDA receptors via competitive binding assays (column 24, lines 64+). Also these antagonists may have high antagonist potency/binding at the kainite, etc.

receptors in addition to the glycine receptor (column 46, lines 39-41). The kainite receptor (glutamate receptor) being an ionotropic receptor that responds to the neurotransmitter glutamate and which has subunits, GluR5, GluR6 and GluR7.

10. Applicant asserts that Freyne et al. describes compounds that exhibit inhibition activity against phosphodiesterase isoenzymes.

11. The reference of Freyne et al. was not used to teach of the binding of the antagonist to the glutamate receptor but that quinoline intermediate compounds may contain monoacylsubstitution on the C-6 position of the naphthyl ring. Cai et al. teaches that the C5-C8 positions of the naphthyl ring may contain an acylamino group and the C8 position may be hydrogen. Both antagonist structures contain a quinoline ring core structure and therefore it would have been obvious to one ordinarily skilled in the art to use the combination of the disclosures to utilize different substituents, such as those disclosed by Freyne et al. (US 5,541,325), on the naphthyl ring of the radiolabeled compounds of Cai et al. (US 5,597,922) to provide for more selective drug ligands to bind to the desired binding site.

12. Claims 1-4,6-9,15 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cai et al. (US 5,597,922) in view of Mabire et al. (WO02/28837A1) as stated in the office action mailed 1/8/07. The modified rejection is necessitated by the amendment to the claims.

13. Applicant asserts that Cai et al. describes compounds that exhibit glycine receptor antagonist activity.

14. Cai et al. teaches of the glutamate/NMDA receptors which bind both glycine and glutamate as well as their antagonists (column 1, lines 41-43). The binding of the glycine receptor antagonists of the disclosure is a diagnostic method for detecting the presence of NMDA receptors via competitive binding assays (column 24, lines 64+). Also these antagonists may have high antagonist potency/binding at the kainite, etc. receptors in addition to the glycine receptor (column 46, lines 39-41). The kainite receptor (glutamate receptor) being an ionotropic receptor that responds to the neurotransmitter glutamate and which has subunits, GluR5, GluR6 and GluR7.

15. Applicant concedes that Maibre et al. discloses compounds that bind to the glutamate receptor but asserts that Maibre et al. contains no teaching or suggestion regarding the radiolabeling of such compounds.

16. The reference of Maibre et al. was not used to teach of the radiolabeling of the antagonists that bind to the glutamate receptors. Cai et al. was used to teach of the radiolabeling of such antagonists. The characterization of binding sites in vitro is difficult and the use of radiolabeled derivatives aid in the characterization via detection of radioactive atoms.

New Grounds of Rejection Necessitated by the Amendment to the Claims

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

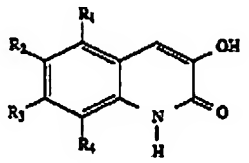
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claims 1-4,6-9,11,13-15 and 17-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mabire et al. (WO02/28837A1) in view of Cai et al. (US 5,597,922) and in further view of Olney et al. (US 5,958,919).

19. Mabire et al. (WO02/28837A1) discloses pure stereoisomeric forms of the quinoline and quinolinone derivatives and their use in medicine (p1, lines 4-6; p2-5; p25, line 10). The quinoline and quinolinone derivatives show mGluR1 antagonistic activity and in the treatment or prevention of glutamate-induced diseases by administering the compounds to mammals (p26, lines 2 and 7-29). The compounds of the disclosure encompass those of the instant claims, such as the R^1-C(=X) moiety may be linked to another position than the 7 or 8 position, thus anticipating position 6 (p5, line 1). Mabire et al. does not disclose radiolabeling the quinoline and quinolinone derivatives.

20. Cai et al. (US 5,597,922) discloses the radiolabeled quinolinone compounds (below) (column 5, lines 60+).



21. These quinolinone compounds are antagonists at the glycine binding site found on the NMDA receptor, which is also a glutamate receptor (column 4; column 1, lines 20-24). Also these antagonists may have high antagonist potency/binding at the kainite, etc. receptors in addition to the glycine receptor (column 46, lines 39-41). The kainite receptor (glutamate receptor) being an ionotropic receptor that responds to the

neurotransmitter glutamate and which has subunits, GluR5, GluR6 and GluR7. The in vitro characterization/determination of the glycine binding site on the glutamate receptor involves isotopically labeling such quinolinone compounds with a ^{3}H, ^{11}C, ^{18}F, etc. at one or more atoms of the compounds (column 57, lines 33-39). Pharmaceutically acceptable aqueous formulation of the compounds may be administered to any animal for such determinations (column 55, lines 51-65; column 57, lines 19-21).

22. Olney et al. (US 5,958,919) discloses the administration of NMDA antagonist drugs to humans for the method of treating Alzheimer's disease (abstract). NMDA receptors are one major class of GLU receptors as are the kainic acid (KA) receptors (column 3, lines 17-31). The NMDA antagonist drug are administered to the brains of laboratory animals to protect the brain tissue against acute excitotoxic damage where the damage is being created by overexcitation of the NMDA receptors by glutamate (column 6, lines 42-45; column 15, lines 5-14; column 16, line 54). When the NMDA receptors are impaired or destroyed the restraining action will be abolished and neuronal degeneration occurs (column 9, lines 43-53). The NMDA antagonist may be administered to treat this impairment (column 13, lines 8-11; column 12, lines 38-42) or a radioactively labeled analog may be administered in order to monitor/image the brain activity. One type of scan used to monitor brain activity via the administration of a radiolabeled NMDA antagonist includes PET which highlights the areas of increased neuronal receptor binding or neuronal activity (column 11, lines 8-23). It is also disclosed that the proper screening/receptor binding assays in in vitro experiments (column 40, lines 55+) can determine suitable analogs having alternate substituents at

certain locations in any of the molecules which would provide neurologists with an improved array of options for treating Alzheimer's patients and the neurologist would be able to select an agent which has the best combination of receptor binding affinities for any specific patient (column 17, lines 66+; column 18, lines 1-9).

23. At the time of the invention it would have been obvious to one ordinarily skilled in the art to radiolabel the quinoline and quinolinone derivatives of Mabire et al. as is disclosed by Cai et al. to provide for the in vitro characterization of binding sites via detection of radioactive atoms. This characterization is often difficult and the use of radiolabeled derivatives aid in the characterization. The combined disclosures generate radiolabeled compounds that bind the mGluR1 receptor and provide an easier determination/characterization of the mGluR1 receptor site of a subject, organ, tissue, etc. via well-known detection/imaging techniques, such as PET (Olney et al.). The radiolabeling of such antagonists can be utilized not only for the treatment of patients at the presymptomatic stage of Alzheimer's disease but allow for the visualization of the brain activity in such patients. This data provides for desirable information into the mechanism of the disease.

Conclusion

No claims are allowed at this time.

24. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Melissa Perreira whose telephone number is 571-272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MP
May 8, 2007

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER